Overview

Theodore B. VanItallie

IT HAS BEEN estimated that, by 2030, the proportion of individuals 65 years of age and older in technologically developed nations will have increased by as much as 50% over the present. The medical, economic, and political implications of this demographic transformation are profoundly unsettling. As Hamet and Tremblay state in this *Metabolism* supplement on aging, "The quest continues to understand the mechanisms of healthy aging, one of the most compelling areas of research in the 21st century."

The articles published herein inform and illuminate this urgent quest. Although "healthy aging" is a goal we all seek, it can only be approached by obtaining an improved understanding of what goes wrong when we age. Why do so many elderly persons prematurely lose strength, endurance, and resilience? Why do their cognitive skills wane and their memory retrieval skills become disablingly impaired? Why do their multiple medications increasingly become a cause for concern? Must these deteriorations—and others that plague the elderly—be accepted as inevitable, or are there potentially effective measures that can be taken to prevent or delay their occurrence?

The present supplement, entitled *Aging: Beneficial Effects on Patients From Recent Advances in Genetics, Neurobiology, and Physiology*, is the outgrowth of a Colloquium of the same title, held under the auspices of the Collège International de Recherche Servier (CIRS) at the Chantecler Hotel in St. Adèle, Quebec, October 2-6, 2002. One of the Collège's major goals is to highlight for clinicians and public health worker's various health problems of global importance. Of these, aging is surely one of the most prominent. At the St. Adèle meeting, a number of important facets of aging were examined and discussed by a group of invited scientists from the United States, Canada, and France, with emphasis on recent advances in medical research and the resulting opportunities for improved diagnosis and treatment. Both the Colloquium and this supplement to *Metabolism* were generously sponsored and supported by CIRS, under the skillful leadership of its President, M. Derôme-Tremblay, PhD. Articles in the supplement summarize important aspects of the genetics, neurobiology, endocrinology, and pharmacology of growing old, as well as certain clinical effects of unhealthy aging.

In his sage and eloquent Introduction, Lenfant refers to the 30-year increase in longevity that has occurred in the United States during the last century, concluding that this remarkable prolongation of life has resulted from positive environmental and sociological influences and their impact on our biology. This improvement is not unique to the United States—nearly all countries have witnessed such gains and some have surpassed the US by a considerable margin. As Lenfant points out, the science of aging is relatively new, but since the creation of the National Institute of Aging in 1974, an enormous amount of knowledge about aging has been acquired. In his words, "Aging is not a disease, it is a part of our normal life, and developing a scientific perspective on it can only make coping with it easier."

In their paper entitled *Genes of Aging*, Hamet and Tremblay take note of evidence that aging is not only controlled by genes, but also by environmental and epigenetic influences that predominate in the second half of life. They call attention to the close link between life span and resistance to stress, and the hypothesis that macromolecule oxidative damage accumulates with age and may be an important determinant of life expectancy. They cite Medawar's provocative insight that natural selection can only take place during the reproductive age—leaving the elderly evolutionarily neglected! Diet-genotype interactions may play an important role in healthy aging. Limitation of caloric intake prolongs life in *Drosophilia*; moreover, the drug 4-phenylbutyrate also lengthens *Drosophilia* life span. The authors have observed reduced DNA half-life in the heart, kidney, and aorta of the spontaneously hypertensive rat (SHR) and propose that this accelerated turnover rate of cardiovascular cells may give rise to more rapid organ damage. Although one might think that "genes are destiny," the observations of Hamet and Tremblay (and others) give grounds for hope that genetic determinants are, to some extent, subject to environmental modulation. In the future, appropriate environmental manipulations (including suitable changes in diet) may not only prolong life, but help make the aging process healthier.

In his discussion of resilience in aging, McEwen suggests that variations in rate of aging may be partly attributable to differences in the severity of wear-and-tear effects imposed on the body by daily experiences and major life stressors. These environmental factors interact with the genetic constitution and with the formative influences on development of early life experiences. His focus is on the disposition of the body to maintain physiological stability in the face of a variety of environmental challenges. This adaptive process is referred to as *allostasis*, which means "maintaining stability through change." He points out that physiological mediators such as adrenalin, glucocorticoids, and cytokines act on receptors in tissues and organs in ways that help the organism adapt to stress in the short term. However, if the release of mediators is not ended after an appropriate period of time, their effects can become damaging to the organism. McEwen uses the term "allostatic load" to describe the price a tissue or organ pays for an overactive or unduly prolonged allostatic response.

Miller and O'Callaghan describe how the hippocampus—a key brain structure for cognition and the feedback control of the stress response—changes with age. Although shrinkage of the aging hippocampus may occur to some extent in humans, it does not

From the Division of Endocrinology, Diabetes, and Nutrition, Medical Service, St. Luke's-Roosevelt Hospital Center; and the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY.

Address reprint requests to Theodore B. VanItallie, MD, PO Box 775, Boca Grande, FL 33921.

0026-0495/03/5210-2002$30.00/0

doi:10.1053/S0026-0495(03)00292-0

appear to undergo a generalized loss of cells or synapses. Therefore, age-related cognitive impairments may be related to changes in the functional (rather than the anatomic) capacity of this structure, including changes in signaling and information encoding properties. The authors point out that, while excessive glucocorticoids can adversely affect cognition as well as hippocampal integrity, these changes are not inevitable concomitants of aging. In the authors' words, "The general preservation of cells and the plastic potential of the hippocampus provide a focus for the development of pharmacological, nutritional, or life style strategies to combat age-related declines."

In his analysis of the effect of aging on the body's vascular system, Plante calls attention to the importance of segments of the vascular system that contain the largest fraction of the blood volume; namely, the microcirculation networks—capillaries and postcapillary venules—in which more than 50% of the entire vascular volume is contained. He points out that the heterogeneous characteristics of these networks with respect to volume and composition may explain the variations in target organ damage associated with a diverse array of vascular diseases such as arterial hypertension, chronic uremia, and congestive heart failure. The primary abnormality common to these diverse disorders seem to be the endothelial dysfunction found in capillary and postcapillary networks. Enhanced endothelial permeability to albumin—leading to extravasation of plasma into the adjacent interstitial compartments—exists in conditions as different as diabetes mellitus, heart failure and vascular aging. The result is an interstitium modified in size and composition and associated with disturbances in the traffic of fluid and vital substrates to organs and interference with removal of waste products in the opposite direction. Based on this model of endothelial damage related to aging and illness, Plante believes that a high research priority for the future should be the creation of novel pharmacologic interventions designed to prevent or ameliorate vascular endothelial damage, especially in microcirculation networks. He also recommends development of noninvasive methods to enhance evaluation of the structure and function of large arterial conduits—particularly in the elderly—and thereby facilitate early detection of vascular rigidity.

In his review of drug therapy for the elderly, Noble describes the effects of aging on drug absorption, distribution, metabolism and elimination in the body. Because of the age-related reductions that occur in saliva, gastric, and small-intestinal fluids, drugs tend to be absorbed at a slower rate in the elderly. This decrease in absorption is augmented by age-associated decreases in jejunal surface area and reductions in splanchnic blood flow. With aging, total systemic perfusion of organs such as the liver and kidneys diminishes. This reduction in organ perfusion decreases the body's ability to metabolize and excrete drugs. As people get older they gain fat and lose fat-free mass, principally muscle. For fat-soluble drugs such as diazepam and thiopental the distribution space increases with aging, leading to their accumulation in adipose tissue, and an unduly prolonged duration of action. For water-soluble drugs like digoxin, with its narrow therapeutic range, there is a decrease in the volume of distribution associated with an increased risk of toxicity resulting from too high blood concentrations. Most drugs are metabolized or detoxified in the liver. In the elderly, hepatic blood flow may decrease by as much as 40%; moreover, some of the liver mechanisms involved in detoxificaton become less efficient with age. Older people use more drugs, increasing the chances of drug reactions and interactions. Because of cognitive decline, elderly persons may become confused and forgetful about their prescribed medications.

As the proportion of the elderly individuals in the population rises, the syndrome of frailty becomes ever more common. In his discussion of the contributions of sarcopenia and visceral protein depletion to frailty, VanItallie enumerates the signs, symptoms, and biological correlates that characterize this disorder. Patients afflicted with frailty look fragile, diminished, and vulnerable. They exhibit muscular weakness, a slow, unsteady gait, fatigue easily, and are extremely sedentary. They are more likely than the nonfrail to fall and, if they fall, to have a fracture. They frequently experience unintentional weight loss, and have a higher risk than the nonfrail of being depressed, having impaired cognition and developing a coexistent illness. They die sooner. They suffer from muscle atrophy (probably caused in large part by disuse), osteopenia, a rise in inflammatory cytokines, and a reduction in the secretion of such anabolic hormones as growth hormone and insulin-like growth factor-1. Because of diminished appetite and dysphoria, elderly people often eat poorly and may develop a degree of protein-calorie malnutrition (PCM), which can be evaluated by means of serial measurements of the "visceral proteins" such as transthyretin, retinol-binding protein, and albumin. Frailty is distinguishable from the effects of aging per se by the potential reversibility of many of its features. Thus, progressive resistance training can increase muscle mass and strength—even in nonagenarians—and thereby reverse important aspects of physical frailty. For individuals who exhibit visceral protein deficiency consumption of a more nutritious diet may engender significant clinical improvement.

In 1999, Alzheimer's disease (AD) was the 8th leading cause of death in the United States among men and women of all ages. Among women aged 85 years and over, it ranked 5th; among men aged 85 years and over, it ranked 6th. In Kalia's discussion of dysphagia and aspiration pneumonia in patients with AD, she reminds us of the growing menace of this devastating illness, pointing out that, unless some way can be found to prevent or effectively treat AD, it will become America's principal public health problem by the middle of the 21st century, with as many as 14 million victims requiring varying degrees of care and supervision. As the dementia of AD progresses, the patients begin to have difficulty in swallowing and may become anorexic. Such oropharyngeal swallowing abnormalities are more prevalent in AD patients than in normal elderly individuals. As Kalia puts it, "The consequences of dysphagia are generally underrated and range from an alteration in the quality of life, dehydration, undernutrition, asphyxia, congestion, and recurrent respiratory tract infections to aspiration pneumonia and death." Because pneumonia is a major cause of death in AD patients and can give rise to obvious and severe suffering—even in severely demented patients—the physician is faced with the dilemma of relieving suffering while, at the same time, attempting to avoid its prolongation. It is therefore important to be able to reliably identify patients at high risk of discomfort and to treat it effectively and appropriately, keeping in mind the special circumstances that surround advanced dementia.